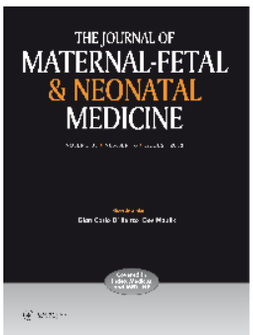

The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: http://www.tandfonline.com/loi/ijmf20

Accuracy of diagnosis and counseling of fetal brain anomalies prior to 24 weeks of gestational age

Rozemarijn Snoek, Marieke E. W. A. Albers, Eduard J. H. Mulder, Klaske D. Lichtenbelt, Linda S. de Vries, Peter G. J. Nikkels, Inge Cuppen, Lourens R. Pistorius, Gwendolyn T. R. Manten & Roel de Heus

To cite this article: Rozemarijn Snoek, Marieke E. W. A. Albers, Eduard J. H. Mulder, Klaske D. Lichtenbelt, Linda S. de Vries, Peter G. J. Nikkels, Inge Cuppen, Lourens R. Pistorius, Gwendolyn T. R. Manten & Roel de Heus (2018) Accuracy of diagnosis and counseling of fetal brain anomalies prior to 24 weeks of gestational age, The Journal of Maternal-Fetal & Neonatal Medicine, 31:16, 2188-2194, DOI: 10.1080/14767058.2017.1338258

To link to this article: https://doi.org/10.1080/14767058.2017.1338258

Accepted author version posted online: 06 Jun 2017.
Published online: 04 Jul 2017.

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
2018, VOL. 31, NO. 16, 2188–2194
https://doi.org/10.1080/14767058.2017.1338258

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Accuracy of diagnosis and counseling of fetal brain anomalies prior to 24 weeks of gestational age

Rozemarijn Snoek[a], Marieke E. W. A. Albers[a], Eduard J. H. Mulder[a], Klaske D. Lichtenbelt[b], Linda S. de Vries[a], Peter G. J. Nikkels[c], Inge Cuppen[d], Lourens R. Pistorius[e,f], Gwendolyn T. R. Manten[a] and Roel de Heus[a]

[a]Department of Obstetrics, University Medical Center Utrecht, Utrecht, The Netherlands; [b]Department of Biomedical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands; [c]Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands; [d]Department of Neurology, University Medical Center Utrecht, Utrecht, The Netherlands; [e]Department of Obstetrics and Gynecology, Tygerberg Hospital, Cape Town, South-Africa; [f]Department of Medicine, University of Stellenbosch, Stellenbosch, South-Africa

ABSTRACT

Objective: To evaluate the accuracy of prenatal neurosonography in diagnosing underlying causes of fetal ventriculomegaly, posterior fossa anomalies and microcephaly before 24 weeks' gestational age (GA) and to study the accuracy of prenatal counseling on postnatal prognosis.

Methods: A retrospective cohort study based on 146 cases of these fetal brain anomalies before 24 weeks' GA. Counseling on prognosis was compared with postnatal outcome. Data on genetic testing was analyzed.

Results: Out of 146 cases, 135 (92%) were diagnosed correctly before 24 weeks' GA. Accuracy was 98% (97/99) in cases with multiple anomalies and 81% (38/47) in cases with an isolated abnormality. Counseling on prognosis was correct in 143 out of 146 cases (98%). Prenatal genetic diagnostics detected an anomaly in 51/113 (45%) of cases. In 14/62 (23%) cases prenatal karyotyping was normal, but postnatal array-CGH detected a pathogenic anomaly.

Conclusions: Despite the challenges of early gestation, accuracy in diagnosing and counseling fetal brain anomalies before 24 weeks' GA was high. Prenatal genetic testing is a valuable diagnostic tool and should be offered to all women with fetal brain anomalies. Considering the many different types of anomalies and diverse etiologies, a multidisciplinary approach is essential for counseling on postnatal outcome.

ARTICLE HISTORY
Received 14 April 2017
Revised 29 May 2017
Accepted 31 May 2017

KEYWORDS
Fetal ultrasound; microcephaly; prenatal counseling; prenatal diagnosis; posterior fossa anomaly; ventriculomegaly

Introduction

Since 2007, all pregnant women in the Netherlands are offered a standardized structural ultrasound scan at 18–22 weeks gestational age (GA) [1]. Over 95% of the Dutch population participates in this screening. If the 20-week anomaly scan raises suspicion of structural fetal anomalies, patients are referred to a tertiary care center for an advanced ultrasound examination, including detailed neurosonography. A multidisciplinary team consisting of perinatologists, geneticists, neonatologists, and pediatric neurologists provides counseling.

Ventriculomegaly (VM), posterior fossa anomalies (PFA), and microcephaly (MC) are among the most common ultrasound findings suggestive of brain pathology. Along with their underlying causes they encompass the majority of fetal brain anomalies.

VM can be an indicator of altered cerebrospinal fluid flow. This may result from obstruction of flow due to pressure effect of arachnoid cysts or aqueductal stenosis, genetic syndromes, developmental disorders (e.g. arterio-venous malformation; agenesis of the corpus callosum), or acquired malformations (e.g. infection or hemorrhage) [2].

PFA comprise various malformations which are often associated with genetic abnormalities. Examples are Dandy–Walker malformation, vermian hypo- or aplasia, persistent Blake's pouch, mega cisterna magna, cerebellar hypoplasia, and acquired disorders such as cerebellar hemorrhage [3].

MC can be due to many underlying etiologies, ranging from genetic abnormalities (e.g. monogenetic disorders and microdeletion syndromes) to migrational disorders as well as metabolic or infectious diseases [4].

CONTACT R. de Heus r.deheus-2@umcutrecht.nl Wilhelmina Kinderziekenhuis, KE.04.123, 3584 EA, Utrecht, The Netherlands

Diagnosing fetal brain anomalies, associated anomalies and genetic causes prior to 24 weeks GA can be challenging. However, accurate diagnosis of abnormalities before this GA is of great importance, since the legal limit for termination of pregnancy (TOP) in the Netherlands is at a GA of 24 weeks [5].

The first aim of this study is to evaluate the diagnostic accuracy of prenatal neurosonography in diagnosing the underlying causes of fetal VM, PFA and MC prior to 24 weeks' GA. The second aim is to study the accuracy of prenatal counseling for postnatal prognosis, based on prenatal ultrasound examinations.

Materials and methods

Prenatal assessment

A retrospective cohort study was performed based on data collected on fetal ultrasound scans obtained between January 2007 and January 2014 in the level three Fetal Medicine Unit of the Wilhelmina Children's Hospital (WKZ), The Netherlands. Patients were included if the prenatal diagnosis of VM, PFA or MC was made prior to 24 weeks' GA and delivery took place in the WKZ. Cases were excluded if there was no data on postnatal diagnosis. All the cases received multiple detailed neurosonography scans prior to 24 weeks' GA, all according to the ISUOG fetal brain assessment guidelines and viral and genetic testing was offered [6].

Cases of VM, i.e. width of lateral ventricles >10 mm, were assessed according to established guidelines [7]. Cases of PFA were categorized as a mega cisterna magna, persistent Blake's pouch, Dandy Walker malformation, vermian hypo- or aplasia, or cerebellar hypoplasia [8]. Acquired disorders due to hemorrhage or tumor in the posterior fossa were also included [9]. Microcephaly was defined as a head circumference measurement below the third percentile [10]. Cases in which a placental cause for intrauterine growth restriction was suspected and cases with spina bifida were excluded.

Data on maternal and fetal demographics, and prenatal and postnatal imaging were retrieved from the electronic patient files. Data on prenatal diagnostics such as fetal MRI, viral and genetic testing (karyotyping, FISH, QF-PCR, array-CGH or SNP-array performed on either amniotic fluid or placental villi) was obtained if present.

Postnatal assessment

Prenatal diagnosis was based on prenatal ultrasound findings and genetic testing, which was compared to the postnatal diagnosis. Postnatal diagnosis was based on autopsy reports in cases of neonatal death or TOP and on postnatal MRI or ultrasound, or genetic testing in cases of survival. If the postnatal diagnosis concurred with the prenatal diagnosis, the prenatal diagnosis was classified as "correct", if not it was classified as "incorrect". In cases where the postnatal imaging showed additional anomalies, the case was noted as having "additional anomalies". In some cases the anomalies resolved *in utero* after 24 weeks' GA, which was diagnosed with prenatal ultrasound, these cases were noted as having "resolved anomalies".

Data on neurodevelopmental outcome was also obtained from the pediatric patient files, where the extent of cognitive and motor impairment was noted in accordance with the Bayley Scales of Infant and Toddler Development (third edition, Hartcourt Assessment Inc, San Antonio, TX) or Griffiths Mental Development Scales (Revised, Hogrefe Ltd., Oxford, UK).

All cases with multiple anomalies were postnatally referred to a geneticist.

Parental counseling

The counseling on prognosis prior to 24 weeks' GA was compared to postnatal outcome. Prenatally all patients were discussed in a multidisciplinary team and counseled by a pediatric neurologist. Counseling was tailored to the specific case. For instance, cases with mild VM would generally be counseled as having a relatively favorable prognosis, in contrast with cases displaying associated anomalies. The prenatal counseling considerations were retrieved from the maternal patient file. This information was compared with the postnatal outcome of the neonate, including examinations by a pediatric neurologist, cranial ultrasound or MRI. Although the spectrum of prognosis was discussed with prospective parents, the most likely outcome was used for statistical comparison, namely prenatal prediction of prognosis being favorable, poor or very poor and postnatal outcome being normal (score of 85–115 on Bayley- or Griffiths Scale), favorable (score of 70–85 on Bayley- or Griffiths Scale), poor (score of 55–70 on Bayley- or Griffiths Scale) or very poor (score of <55 on Bayley- or Griffiths Scale).

Statistical analysis

Descriptive statistical analysis was performed using SPSS for Windows (version 21; IBM/SPSS Inc, Chicago, IL): means and ranges for continuous variables, counts and percentages for categorical variables. Patient samples were generally too small to allow for subgroup analysis.

Results

A total of 146 fetuses with brain anomalies diagnosed prior to 24 weeks' GA were identified during the study period. VM was diagnosed in 67 cases, PFA in 62 cases, and MC in 17 cases. The baseline characteristics are presented in Table 1. Figure 1 presents the prenatal diagnostic process, of which the results will be discussed in depth below.

Table 1. Baseline characteristics.

Characteristics	Pregnancies ($n = 146$)
Maternal age (years); Mean (SD)	31 (5)
Termination of pregnancy; *n*/total *n* (%)	69/146 (47%)
Gestational age at delivery[a] (weeks); Mean (SD)	37.3 (4.6)
Birth weight[a] (g); Mean (SD)	3100 (790)
Gender (male); *n*/total *n* (%)	73/146 (50%)
Overall postpartum death[a]; *n*/total *n* (%)	26/77 (34%)
Of which neonatal death[b]; *n*/total *n* (%)	21/26 (81%)

[a]Based on 77 cases, as data on pregnancies that were terminated <24 weeks was not included in these characteristics.
[b]Neonatal death is defined as death within 4 weeks after birth.

Prenatal diagnostic accuracy

Out of 146 cases, 135 (92%) were diagnosed correctly prior to 24 weeks' GA. Namely 97 with multiple anomalies and 38 with isolated anomalies, of which 11 resolved in utero. In 6 cases additional anomalies were found after 24 weeks' GA and in 5 cases the neurosonography diagnosis was incorrect. All these cases will be discussed below.

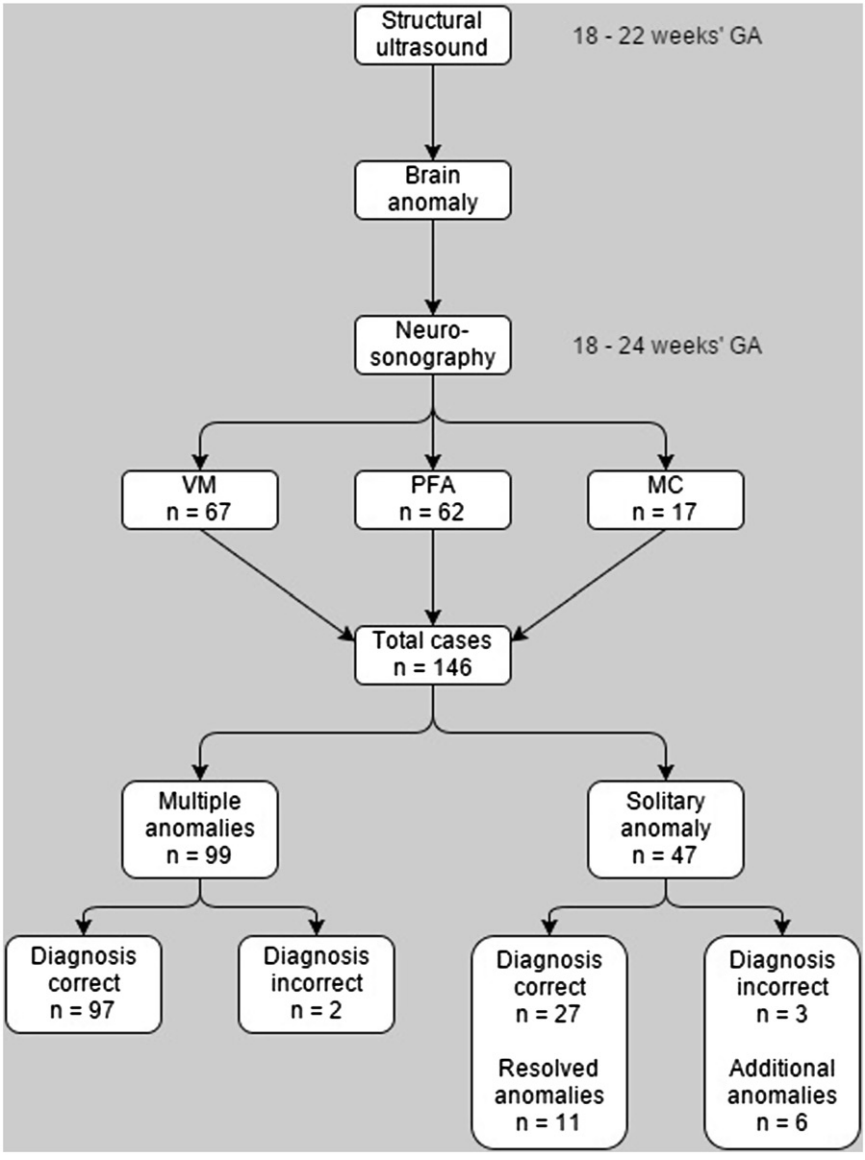

Figure 1. Flowchart of prenatal diagnostic process. Presented by whether prenatal diagnosis was either correct (including cases with resolved anomalies) or incorrect (including cases with additional anomalies). Ventriculomegaly (VM), posterior fossa anomalies (PFA), microcephaly (MC).

When further assessing the ultrasound diagnoses in these cases, we note that the majority of cases ($n = 99$, 68%) had multiple anomalies, including both intra- and extracranial anomalies, of which 97 (98%) were correctly diagnosed. In the 47 cases where an isolated abnormality was suspected, 27 (57%) were diagnosed correctly and 11 (23%) resolved in utero. Therefore, the diagnostic accuracy in cases with an isolated abnormality was ~81% ($n = 38/47$).

First we will discuss the cases that were carried to term and were thus postnatally assessed with either ultrasound or MR imaging. In 77 cases (53%) the pregnancy was carried to term, of which 39 had multiple anomalies and 38 solitary findings. Sixty (78%) of the cases were correctly diagnosed prior to 24 weeks' GA. In 11 cases of solitary anomaly, it resolved *in utero* after 24 weeks' GA and had previously been diagnosed as isolated mild VM ($n = 6$), mild cerebellar hypoplasia ($n = 3$), persistent Blake's pouch ($n = 1$), and mild hemorrhage in the posterior fossa ($n = 1$). Additional (extracranial) anomalies were detected after 24 weeks' GA in 3 cases (4%). In 3 other cases (4%) postnatal imaging showed other underlying causes than prenatally thought. Namely, a prenatal diagnosis of persistent Blake's pouch in 2 cases that were diagnosed postnatally with an isolated vermian aplasia and a retrocerebellar cyst, respectively. Furthermore, one case was prenatally classified as a mega cisterna magna and postnatally as a persistent Blake's pouch.

In $n = 69$ of all 146 cases (47%) parents decided to terminate the pregnancy prior to 24 weeks' GA. Fifty-eight of these cases (84%) were terminated because of multiple intra- and extracranial anomalies on fetal ultrasound, with 33 having a proven genetic aberration. The remaining 11 out of 69 cases (16%) were terminated because of the severity of an isolated anomaly, mainly severe hydrocephaly. Autopsy confirmed the prenatal diagnosis in $n = 64$ (93%). In 3 cases autopsy showed additional anomalies, all terminated because of severe hydrocephaly. At autopsy, the hydrocephaly was confirmed, but also the cause identified. Namely, heterotopias near the foramina of Luschka and Magendie ($n = 1$), aqueductal stenosis in a case without prenatal third ventricle enlargement ($n = 1$) and additional spinal vertebrae deformities ($n = 1$).

In 2 cases of TOP the prenatal diagnosis prior to 24 weeks' GA was incorrect. Namely, a case of a fetus with suspicion of microcephaly with an unknown cause that had a normal head circumference at postnatal inspection (parents did not consent to autopsy). The second case had a small cerebellum, cleft palate and a hyperechogenic bowel on fetal ultrasound, while autopsy only confirmed the cleft palate.

Prenatal counseling on postnatal outcome

All parents were counseled prior to 24 weeks' GA on the expected postnatal outcome, based on the extent and severity of fetal ultrasound anomalies and on the results of genetic and viral analyses if available. Overall, counseling on prognosis was correct in 143 out of a total of 146 cases (98%).

The majority of these, namely, $n = 134$, were in the group of 135 cases that were diagnosed correctly before 24 weeks' GA, including the 26 cases that were predicted not to survive beyond infancy (see Table 1). And although the diagnosis was incorrect in 11 cases, of which 6 cases with additional anomalies found postnatally, counseling on prognosis was correct in 9 of these cases. As mentioned above, in 11 of these cases the brain anomalies resolved in utero after 24 weeks' GA and all these children had a normal neurodevelopmental outcome. Since in these cases that resolved in utero the prognosis had already been predicted to be favorable and possibly normal prior to 24 weeks' GA, the cases can also be considered as correctly counseled for prognosis.

In 3 cases the prenatal counseling was deemed incorrect. This was the case for one fetus with MC and hepatic anomalies, where the postnatal outcome was more favorable than prenatally predicted. Prenatally the possibility of a syndrome diagnosis with an associated poor outcome was discussed, but the child had a normal neurodevelopmental outcome and no underlying (genetic) cause was found. In 2 cases, both with prenatally diagnosed isolated VM, the prenatal counseling had been too favorable, since additional anomalies were found postnatally (a case of perinatal hemorrhage and a case with bowel anomalies due to a trisomy 21 for which the parents opted no prenatal genetic testing) and thus had a worse outcome than prenatally predicted.

MRI, viral and genetic analysis

In many cases the prenatal diagnostic process was aided by diagnostic means other than neurosonography. The results of genetic testing (karyogram, QF-PCR, FISH, array-CGH and SNP-array) in amniotic fluid or placental villi, and viral testing in maternal serum prior to 24 weeks' GA are reported below.

Fetal MRIs were performed, but not prior to 24 weeks' GA. The 34 MRIs made after 24 weeks' GA all confirmed the ultrasound diagnosis, and in cases of

Table 2. Prenatal and postnatal genetic diagnoses (*n*) per main neurosonography anomaly, in order of prevalence.

	Ventriculomegaly	Posterior fossa anomalies	Microcephaly
Prenatal aneuploidies	Partial trisomy 13 ($n = 1$) Partial trisomy, partial monosomy 9 ($n = 1$) Trisomy 18 ($n = 4$) Trisomy 21 ($n = 4$) Trisomy X ($n = 1$)	Mosaic variegated aneuploidy ($n = 1$) Partial trisomy 13 ($n = 1$) Tetraploidy 9 ($n = 1$) Triploidy ($n = 3$) Trisomy 13 ($n = 7$) Trisomy 18 ($n = 4$) Trisomy 21 ($n = 2$) Trisomy 9 ($n = 2$)	Trisomy 18 ($n = 2$) Trisomy 21 ($n = 1$)
Prenatal structural variants	1q21.1 deletion ($n = 1$) 7q11.23 duplication ($n = 1$) 7q36.1 duplication ($n = 1$) Balanced Robertsonian translocation ($n = 1$)	18p11.3 duplication ($n = 1$) 7q36.1 duplication ($n = 1$) 8q21.3 duplication ($n = 1$) Multiple deletions and duplications ($n = 2$) Terminal 4p deletion, terminal 17p duplication ($n = 1$) Xp22.12 duplication ($n = 1$)	Distal 18q deletion ($n = 1$)
Prenatal missense mutations	Homozygous *POMT2* mutation ($n = 1$)	Homozygous *POMT2* mutation ($n = 1$)	Épsilon-gamma-delta-bèta-zero thalassemia ($n = 1$) Pyruvate dehydrogenase deficiency c ($n = 1$)
Postnatal aneuploidies	Trisomy 21 ($n = 1$)		
Postnatal structural variants	1q36 deletion ($n = 1$)		
Postnatal missense mutations	Delleman-Oorthuis syndrome ($n = 1$) Ehlers-Danlos VI B syndrome ($n = 1$) Goldenhar syndrome ($n = 1$) Gorlin syndrome ($n = 1$) Joubert-like syndrome ($n = 1$) Simpson-Galabi-Behmel syndrome ($n = 1$) VACTERL association ($n = 1$)	ALG12-congenital disorder of glycosylation ($n = 1$) CHARGE syndrome ($n = 1$) Cockayne syndrome ($n = 1$) Ehlers-Danlos VI B syndrome ($n = 1$) Molybdene cofactor deficiency ($n = 1$)	

severe anomalies it provided information on the extent of the anomalies.

Viral testing was performed in 63 cases, of which 2 showed an active infection. One was in a case of MC with signs of a cytomegalovirus infection on fetal ultrasound, which was proven by maternal high serum IgM. One isolated VM case tested positive for toxoplasmosis. Maternal prenatal treatment was commenced and the fetus had no VM at birth and showed a normal neurodevelopmental outcome.

In 113 cases genetic testing was performed, of which 51 showed a genetic anomaly. All genetic anomalies found pre- and postnatally are shown in Table 2. The majority of genetic tests ($n = 90$, 80%) was done in cases with associated anomalies, which was also the group with the most found genetic aberrations ($n = 50/51$, 98%). There were two other major groups that underwent prenatal genetic testing, namely, isolated VM ($n = 6$, 5%), cases of severe VM with suspicion of aqueductal stenosis ($n = 6$, 5%) and a for miscellaneous indications ($n = 11$, 10%). In one case of isolated mild VM a balanced Robertsonian translocation was found.

In the remainder of cases where prenatal genetic testing was performed ($n = 62$), the test showed a normal karyogram, QF-PCR or FISH. In 14 of these cases (23%), a chromosomal anomaly was found postnatally with array-CGH or SNP-array. In all these cases multiple structural anomalies were seen on prenatal ultrasound, which postnatally proved to be diagnosed correctly. However, an exact syndromic diagnosis could not be made prenatally, since array-CGH was not yet used prenatally at our hospital when those particular cases were included.

In 4 cases, of which 3 had an incorrect prenatal diagnosis and 1 case had postnatally diagnosed associated anomalies, parents did not opt for genetic testing. Even though multiple anomalies were present at birth in these cases, postnatally no genetic aberration was found.

Discussion

In the Netherlands, the legal limit for TOP is 24 weeks' GA [5]. Therefore, in case of detection of fetal anomalies, an accurate diagnosis and a careful counseling process prior to this gestational age limit is crucial. Our study shows that the overall accuracy of diagnosing VM, PFA, MC and associated fetal brain anomalies prior to 24 weeks' GA is 92%. The counseling of expectant parents on postnatal outcome was correct in 98%. This allows a basis to make a well-informed decision on whether or not to continue the pregnancy, even in the second trimester.

The accuracy of fetal ultrasound reported in the literature differs enormously. The overall accuracy of ultrasound when compared to autopsy is around 77%, while for separate underlying causes accuracy can be as low as 30% and as high as 100% [2,11–19]. The reported variation in accuracy rates is due to the heterogeneity of the underlying causes discussed in these papers, from acquired infections to genetic predispositions and disruptions in various brain structures. Many studies have reported on the accuracy of one specific anomaly, such as Dandy–Walker malformation, which differs significantly from the diagnostic process in case of agenesis of the corpus callosum [18,20]. Also, the severity of the anomalies included differs between studies.

Posterior fossa anomalies such as persistent Blake's pouch, cerebellar and vermian hypo- or aplasia are more challenging to diagnose accurately prior to 24 weeks [21,22]. Gandolfi Colleoni et al. noted that structures in the posterior fossa, such as the vermis, are often difficult to assess in early gestation [23]. One could argue that as the fetal brain develops, brain abnormalities become easier to diagnose.

In case of VM, which is an ultrasound sign rather than a disease in itself, diagnosis of underlying pathology in utero is challenging both before and after 24 weeks' GA. Counseling on the prognosis of VM prior to 24 weeks' gestation is hampered by the fact that progressive dilatation in the third trimester cannot reliably be predicted, while this is the only significant predictor for postnatal major brain abnormalities in cases of isolated VM. [2,14,24].

However, despite the challenges of early gestation and early stage brain development overall diagnostic accuracy rate in this study was 92% prior to 24 weeks' GA. Counseling on postnatal prognosis was accurate in 98% prior to 24 weeks' GA, even though the neurodevelopmental outcome can vary greatly depending on the severity of the anomalies, the presence of associated anomalies or a genetic diagnosis [23,25–27].

To aid the prenatal diagnostic process, which begins with a fetal ultrasound examination, additional fetal MRI and genetic testing in amniotic fluid or placental villi can be helpful. In this cohort no MRIs were made prior to 24 weeks' GA. Therefore, we cannot comment on the additional value of MRI before this GA. MRIs performed after 24 weeks' GA all confirmed the ultrasound diagnosis, and provided additional information on the extent of the abnormalities. Previous authors have also shown that MRI could offer clinically relevant findings, especially after 24 weeks' GA [28–30].

During the study period (2007 through 2014) different types of genetic analysis, with increasing resolution, have been applied. In cases included from 2007 only standard karyotyping, FISH and QF-PCR could be performed prenatally, while as of 2012 array-CGH became available. With the introduction of SNP-array this has become the method of first choice for invasive prenatal testing in our center since 2014 [31]. It is especially useful for brain anomalies, as SNP-array can yield a genetic aberration in 37% of fetal brain anomaly cases [32]. One should note that of the 14 cases in which the genetic aberration causing the ultrasound anomalies was only found postnatally, 13 of these had a missense mutation, which cannot be detected by SNP-array.

The main limitation of this study is its retrospective design. Second, it is a monocenter study on inborn infants referred to a tertiary center, which leads to a highly selected population. All fetuses with minor anomalies were referred back to the referring caregivers. Since there was no consistent pediatric follow-up of these cases, they were excluded. Therefore, the majority of cases included in this study were either severe anomalies or cases with multiple anomalies, which may have influenced the high accuracy number since these anomalies are easier to diagnose.

In conclusion, despite the challenges of early gestation and early stage brain development the overall accuracy rate in diagnosing and providing accurate prognosis on fetal brain anomalies prior to 24 weeks' GA was high, especially in cases with severe anomalies. Prenatal genetic testing is a valuable diagnostic tool and should be offered to all women with fetal brain anomalies. Considering the many different types of anomalies and diverse etiologies, a multidisciplinary approach is essential for accurate prenatal diagnosis of fetal brain anomalies as well as for counseling on postnatal outcome.

Disclosure statement

The authors report no conflicts of interest.

References

[1] The Dutch Society of Obstetrics and Gynaecology (NVOG), Modelprotocollen - Structureel Echoscopisch Onderzoek (SEO) 2.0. Dutch Standards of Routine Ultrasound Examination. Nederlandse Vereniging voor Obstetrie en Gynaecologie; 2012.

[2] Pisapia JM, Sinha S, Zarnow DM, et al. Fetal ventriculomegaly: diagnosis, treatment, and future directions. Childs Nerv Syst. 2017. [Epub ahead of print]. doi: 10.1007/s00381-017-3441-y

[3] Paladini D, Volpe P. Posterior fossa and vermian morphometry in the characterization of fetal cerebellar abnormalities: a prospective three-dimensional ultrasound study. Ultrasound Obstet Gynecol. 2006;27:482–489.
[4] Abuelo D. Microcephaly syndromes. Semin Pediatr Neurol. 2007;14:118–127.
[5] Jaarrapportage 2013 Van de Wet afbreking zwangerschap. Utrecht, The Netherlands, December 2014. (Report of the Dutch Ministry of Health on termination of pregnancy).
[6] International Society of Ultrasound in Obstetrics & Gynecology Education Committee. Sonographic examination of the fetal central nervous system: guidelines for performing the "basic examination" and the 'fetal neurosonogram'. Ultrasound Obstet Gynecol. 2007;29:109–116.
[7] Cardoza JD, Goldstein RB, Filly RA. Exclusion of fetal ventriculomegaly with a single measurement: the width of the lateral ventricular atrium. Radiology. 1988;169:711–714.
[8] Shekdar K. Posterior fossa malformations. Ultrasound CT MR. 2011;32:228–241.
[9] Chapman T, Mahalingam S, Ishak GE, et al. Diagnostic imaging of posterior fossa anomalies in the fetus and neonate: part 2, Posterior fossa disorders. Clin Imaging. 2015;39:167–175.
[10] Kurtz AB, Wapner RJ, Rubin CS, et al. Ultrasound criteria for in utero diagnosis of microcephaly. J Clin Ultrasound. 1980;8:11–16.
[11] Carroll SG, Porter H, Abdel-Fattah S, et al. Correlation of prenatal ultrasound diagnosis and pathologic findings in fetal brain abnormalities. Ultrasound Obstet Gynecol. 2000;16:149–153.
[12] Chervenak FA, Rosenberg J, Brightman RC, et al. A prospective study of the accuracy of ultrasound in predicting fetal microcephaly. Obstet Gynecol. 1987; 69:908–91.
[13] Gandolfi Colleoni G, Contro E, Carletti A, et al. Prenatal diagnosis and outcome of fetal posterior fossa fluid collections. Ultrasound Obstet Gynecol. 2012;39:625–631.
[14] Paladini D, Pastore G, Cavallaro A, et al. Agenesis of the fetal corpus callosum: sonographic signs change with advancing gestational age. Ultrasound Obstet Gynecol. 2013;42:687–690.
[15] Woods CG, Basto R. Microcephaly. Curr Biol. 2014;24:R1109–R1111.
[16] Griffiths PD, Brackley K, Bradburn M, et al. Anatomical subgroup analysis of the MERIDIAN cohort: ventriculomegaly. Ultrasound Obstet Gynecol. 2017. [Epub ahead of print]. doi: 10.1002/uog.17475
[17] Griffiths PD, Brackley K, Bradburn M, et al. Anatomical subgroup analysis of the MERIDIAN cohort: posterior fossa abnormalities. Ultrasound Obstet Gynecol. 2017. [Epub ahead of print]. doi: 10.1002/uog.17485
[18] Phillips JJ, Mahony BS, Siebert JR, et al. Dandy–Walker malformation complex: correlation between ultrasonographic diagnosis and postmortem neuropathology. Obstet Gynecol. 2006;107:685–693.
[19] D'Antonio F, Khalil A, Garel C, et al. Systematic review and meta-analysis of isolated posterior fossa malformations on prenatal ultrasound imaging (part 1): Nomenclature, diagnostic accuracy and associated anomalies. Ultrasound Obstet Gynecol. 2016;47: 690–697.
[20] Craven I, Bradburn MJ, Griffiths PD. Antenatal diagnosis of agenesis of the corpus callosum. Clin Radiol. 2015;70:248–253.
[21] Garel C. Posterior fossa malformations: main features and limits in prenatal diagnosis. Pediatr Radiol. 2010;40:1038–1045.
[22] Malinger G, Lev D, Lerman-Sagie T. The fetal cerebellum. Pitfalls in diagnosis and management. Prenat Diagn. 2009;29:372–380.
[23] Deloison B, Chalouhi GE, Bernard JP, et al. Outcomes of fetuses with small head circumference on second-trimester ultrasonography. Prenat Diagn. 2012;32: 869–874.
[24] Baffero GM, Crovetto F, Fabietti I, et al. Prenatal ultrasound predictors of postnatal major cerebral abnormalities in fetuses with apparently isolated mild ventriculomegaly. Prenat Diagn. 2015;35:783–788.
[25] Bolduc ME, Limperopoulos C. Neurodevelopmental outcomes in children with cerebellar malformations: a systematic review. Dev Med Child Neurol. 2009;51: 256–267.
[26] Gaglioti P, Danelon D, Bontempo S, et al. Fetal cerebral ventriculomegaly: outcome in 176 cases. Ultrasound Obstet Gynecol. 2005;25:372–377.
[27] Ghali R, Reidy K, Fink AM, et al. Perinatal and short-term neonatal outcomes of posterior fossa anomalies. Fetal Diagn Ther. 2014;35:108–117.
[28] Paladini D, Quarantelli M, Sglavo G, et al. Accuracy of neurosonography and MRI in clinical management of fetuses referred with central nervous system abnormalities. Ultrasound Obstet Gynecol. 2014;44:188–196.
[29] Griffiths PD, Bradburn M, Campbell MJ, et al. Use of MRI in the diagnosis of fetal brain abnormalities in utero (MERIDIAN): a multicentre, prospective cohort study. Lancet. 2017;389:538–546.
[30] Frick N, Fazelnia C, Kanzian K, et al. The reliability of fetal MRI in the assessment of brain malformations. Fetal Diagn Ther. 2015;37:93–101.
[31] Srebniak MI, Boter M, Oudesluijs GO, et al. Genomic SNP array as a gold standard for prenatal diagnosis of foetal ultrasound abnormalities. Mol Cytogenet. 2012;5:14.
[32] Sun L, Wu Q, Jiang SW, et al. Prenatal diagnosis of central nervous system anomalies by high-resolution chromosomal microarray analysis. BioMed Res Int. 2015;2015:426379.